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L8: Entry 3 of 3 File: USPT Jul 11, 2000

US-PAT-NO: 6087115
DOCUMENT-IDENTIFIER: US 6087115 A

TITLE: Methods of identifying negative antagonists for G protein coupled receptors

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gershengorn; Marvin C.	New York	NY		
Arvanitakis; Leandros	New York	NY		
Geras-Raaka; Elizabeth	Dobbs Ferry	NY		
Cesarman; Ethel	Hoboken	NJ		

US-CL-CURRENT: 435/7.21; 435/252.3, 435/254.11, 435/325, 435/365, 435/6, 435/69.1, 435/7.2, 435/8, 530/350, 536/23.1, 536/23.72, 536/24.1

CLAIMS:

What is claimed is:

1. A method of identifying a negative antagonist of a constitutively active G protein coupled receptor of human herpesvirus 8, said method comprising:

co-expressing in a host cell a constitutively active G protein coupled receptor of human herpesvirus 8 and a reporter protein, wherein expression

of the reporter protein is controlled by a promoter responsive to a signaling pathway activated by the constitutively active G protein coupled receptor of human herpesvirus 8;

determining a first activity level of the reporter protein;

exposing the host cell to a test substance;

determining a second activity level of the reporter protein after said exposing the host cell to the test substance; and

identifying the test substance, where the second activity level is less than the first activity level, as a negative antagonist of the constitutively active G protein coupled receptor of human herpesvirus 8.

2. The method of claim 1 wherein said promoter is a cyclic AMP-responsive promoter.

3. The method of claim 1 wherein said promoter is a protein kinase C-responsive promoter.

4. The method of claim 1 wherein said reporter protein is luciferase.

5. The method of claim 4 wherein said determining the first and second activity

levels is carried out using a luminescent assay.

6. The method of claim 1 wherein said host cell is a mammalian cell.

7. The method of claim 6 wherein said mammalian cell is a COS cell.

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☐ 1. Document ID: US 6392029 B1

L8: Entry 1 of 3 File: USPT May 21, 2002

US-PAT-NO: 6392029
DOCUMENT-IDENTIFIER: US 6392029 B1

TITLE: HIV chemokines

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6093806 A

L8: Entry 2 of 3 File: USPT Jul 25, 2000

US-PAT-NO: 6093806
DOCUMENT-IDENTIFIER: US 6093806 A

TITLE: DNA encoding proteins of Kaposi's sarcoma associated herpesvirus

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6087115 A

L8: Entry 3 of 3 File: USPT Jul 11, 2000

US-PAT-NO: 6087115
DOCUMENT-IDENTIFIER: US 6087115 A

TITLE: Methods of identifying negative antagonists for G protein coupled receptors

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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PROTEINS.USPT.	88772
COUPLED.USPT.	694999
COUPLEDS.USPT.	2
RECEPTOR.USPT.	55322
RECEPTORS.USPT.	38376
GPCR.USPT.	131
GPCRS.USPT.	110
(5 WITH (GPCR OR (((G ADJ PROTEIN) ADJ COUPLED) ADJ RECEPTOR))).USPT.	3
(L5 WITH (G PROTEIN COUPLED RECEPTOR OR GPCR)).USPT.	3

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Previous Page Next Page

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(L5 NEAR (G PROTEIN COUPLED RECEPTOR OR GPCR)).USPT.	0

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DATE: Monday, November 04, 2002 Printable Copy Create Case

L8: Entry 1 of 3 File: USPT May 21, 2002

DOCUMENT-IDENTIFIER: US 6392029 B1
TITLE: HIV chemokines

Brief Summary Text (12):
Kaposi's sarcoma is an AIDS-related malignancy. The Kaposi's sarcoma-associated herpesvirus (KHSV, human herpesvirus 8) has been shown to encode a chemokine receptor ("GPCR") that is analogous in sequence and chemokine specificity to CXCR2 (Arvantikas et al., 1997, Nature 385:347-349). This is not the only instance in which a virus has apparently pirated a cellular gene encoding either a chemokine or a chemokine receptor. KSHV and Molluscum contagiosum have open reading frames that encode CC chemokines; and Herpesvirus Saimiri, human cytomegalovirus, KSHV, Equine herpesvirus-2, Swine pox virus, and capripox virus have open reading frames encoding chemokine receptors (Murphy, 1997, Nature 385:296-299; Neote et al., 1993, Cell 72:415-425).

Detailed Description Text (23):
Kaposi's sarcoma is a malignancy that is rare in individuals uninfected with HIV, but frequent in (up to 20 percent of) homosexuals with AIDS. Kaposi's sarcoma-associated herpesvirus (KSHV) is thought to be the virus that is the etiologic cofactor of Kaposi's sarcoma in AIDS patients (Kedes et al., 1996, Nat. Med. 2:918-924; Arvanitakis et al., 1997, Nature 385:347-349). Recently, discovered was a chemokine receptor produced by KSHV ("KSHV GPCR") which may act as a cofactor in AIDS-related malignancies including Kaposi's sarcoma and primary effusion lymphoma (PEL) (Arvanitakis et al., 1997, supra). However, the expression of this chemokine receptor on an KSHV-infected cell is not sufficient to lead to altered growth or neoplastic transformation. Rather, signaling of cell-KSHV GPCR is required by a cofactor produced during AIDS pathogenesis before altered growth or neoplastic transformation is initiated. Epidemiologic data supports this scenario, since KSHV appears to be sexually transmitted but malignancy primarily occurs only in AIDS patients; i.e., a sexually transmitted agent leading to AIDS-related malignancy rather than just a sexually transmitted agent leading to malignancy. While chemokines of the CXC class or CC class have been shown to bind to KSHV GPCR (Arvanitakis et al., 1997, supra), a logical cofactor that is HIV-related and thus explains the association between AIDS and malignancies including Kaposi's sarcoma and PEL is the HIV chemokine. That is, the HIV chemokine and KSHV GPCR are cofactors that interact to initiate cell signals leading to altered growth or neoplastic transformation in KSHV-infected cells. To interact with the KSHV GPCR which is membrane bound in the KSHV-infected cells, the HIV chemokine may either be soluble (e.g., secreted from HIV-infected cells), or a component of a viral particle or HIV infected cell membrane (e.g., interacting by itself as a membrane bound receptor or in conjunction with gp120).

L8: Entry 2 of 3 File: USPT Jul 25, 2000

DOCUMENT-IDENTIFIER: US 6093806 A
TITLE: DNA encoding proteins of Kaposi's sarcoma associated herpesvirus

Abstract Text (1):
The present invention is directed to isolated nucleic acid molecules encoding proteins of Kaposi's sarcoma associated herpesvirus, including an antigenic receptor protein, a G protein coupled receptor, and a cyclin protein. Expression vectors and host cells comprising the nucleic acid molecules are also provided, as well as methods for increasing or decreasing the expression of the KSHV proteins in host cells. DNA oligomers and antibodies specific for the KSHV proteins are provided, each of which can be used to detect the KSHV proteins in a sample. Isolated KSHV proteins are also provided.

Brief Summary Text (2):
The present invention relates generally to proteins of Kaposi's sarcoma associated herpesvirus and, more particularly, to an antigenic membrane protein, a G protein coupled receptor, and a cyclin protein of Kaposi's sarcoma-associated herpesvirus, nucleic acid molecules encoding the proteins, and uses thereof.

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L8: Entry 3 of 3 File: USPT Jul 11, 2000

DOCUMENT-IDENTIFIER: US 6087115 A
TITLE: Methods of identifying negative antagonists for G protein coupled receptors

Detailed Description Text (4):
The constitutively active G protein coupled receptor can be any such receptor which one desires to turn off. For example, GPCRs which are tumorigenic or which cause cells to proliferate could be of interest for application of the method of the subject invention. By identifying negative antagonists of such GPCRs, the negative antagonists could be used to turn off the GPCR and thereby eliminate the GPCR's tumorigenic or cell proliferative effects. An example of such a constitutively active GPCR is the GPCR of human herpesvirus 8 (HHV 8) (also known as Kaposi's sarcoma associated herpesvirus or KSHV) (Cesarman et al. 1996).

Other Reference Publication (4):
Cesarman et al., "Kaposi's Sarcoma-Associated Herpesvirus Contains G Protein-Coupled Receptor and Cyclin D Homologs Which Are Expressed in Kaposi's Sarcoma and Malignant Lymphoma," Journal of Virology, 70(11):8218-8223(1996).

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L8: Entry 3 of 3 File: USPT Jul 11, 2000

US-PAT-NO: 6087115
DOCUMENT-IDENTIFIER: US 6087115 A

TITLE: Methods of identifying negative antagonists for G protein coupled receptors

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gershengorn; Marvin C.	New York	NY		
Arvanitakis; Leandros	New York	NY		
Geras-Raaka; Elizabeth	Dobbs Ferry	NY		
Cesarman; Ethel	Hoboken	NJ		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Cornell Research Foundation, Inc.	Ithaca	NY			02

APPL-NO: 08/ 785928 [PALM]
DATE FILED: January 22, 1997

INT-CL: [07] G01 N 33/566, C12 N 15/39, C12 N 5/10, C07 K 14/03

US-CL-ISSUED: 435/7.21; 435/6, 435/7.2, 435/8, 435/69.1, 435/325, 435/365, 435/252.3, 435/254.11, 536/23.72, 536/24.1, 536/23.1, 530/350
US-CL-CURRENT: 435/7.21; 435/252.3, 435/254.11, 435/325, 435/365, 435/6, 435/69.1, 435/7.2, 435/8, 530/350, 536/23.1, 536/23.72, 536/24.1

FIELD-OF-SEARCH: 435/6, 435/7.21, 435/7.2, 435/8, 435/69.1, 435/325, 435/365, 435/252.3, 435/254.11, 530/350, 536/23.72, 536/24.1, 536/23.1

PRIOR-ART-DISCLOSED:

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	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5087564	February 1992	Mai et al.	435/69.7
☐	5384243	January 1995	Gutkind et al.	435/6
☐	5385831	January 1995	Mulvihill et al.	435/69.1
☐	5403484	April 1995	Ladner et al.	435/235.1
☐	5436128	July 1995	Harpold et al.	435/6
☐	5462856	October 1995	Lerner et al.	435/7.21
☐	5476781	December 1995	Moyer et al.	435/240.2
☐	5482835	January 1996	King et al.	435/6
☐	5498530	March 1996	Schatz et al.	435/69.1
☐	5506102	April 1996	McDonnell	435/6
☐	5508384	April 1996	Murphy et al.	530/324
☐	5516889	May 1996	Hollenberg et al.	530/317
☐	5521295	May 1996	Pacifici et al.	536/23.4
☐	5908773	September 1996	Cesarman et al.	
☐	5948676	October 1996	Chang et al.	

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Himmler et al., Journal of Receptor Research, 13, 79-94, 1993.
Eggerickx et al., Biochem. J., 309, 837-843, 1995.
Cesarman et al., "Kaposi's Sarcoma-Associated Herpesvirus Contains G Protein-Coupled Receptor and Cyclin D Homologs Which Are Expressed in Kaposi's Sarcoma and Malignant Lymphoma," Journal of Virology, 70(11):8218-8223(1996).
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Tate et al., "Secreted Alkaline Phosphatase: An Internal Standard for Expression of Injected mRNAs in the Xenopus oocyte," FASEB J., 4:227-231 (1990).
Laakkonen et al., "A Refined Model of the Thyrotropin-Releasing Hormone (TRH) Receptor Binding Pocket. Novel Mixed Mode Monte Carlo/Stochastic Dynamics Simulations of the Complex between TRH and TRH Receptor," Biochemistry, 35(24):7651-7663 (1996).
Gundersen et al., "Neural Regulation of Muscel Acetylcholine Receptor .epsilon.-and .alpha.-Subunit Gene Promoters in Transgenic Mice," J. Cell Biol., 123(6):1535-1544 (1993).
Heinflink et al., "A Constitutively Active Mutant Thyrotropin-Releasing Hormone Receptor Is Chronically Down-Regulated in Pituitary Cells: Evidence Using Chlordiazepoxide as a Negative Antagonist," Mol. Endocrin., 9(11):1455-1460 (1995).
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Cascieri et al., "Molecular Characterization of a Common Binding Site for Small Molecules Within the Transmembrane Domain of G-Protein Coupled Receptors," J. Pharma. and Toxicol. Methods, 33:179-185 (1995).

ART-UNIT: 166

PRIMARY-EXAMINER: Spector; Lorraine

ASSISTANT-EXAMINER: Kaufman; Claire M.

ABSTRACT:

The present invention is directed to a constitutively active G protein coupled receptor of human herpesvirus 8, as well as a method of identifying negative antagonists of a constitutively active G protein coupled receptor. The method comprises co-expressing in a host cell a constitutively active G protein coupled receptor and a reporter protein, wherein expression of the reporter protein is controlled by a promoter responsive to a signalling pathway activated by the constitutively active G protein coupled receptor; exposing the host cell to a test substance; and determining a level of reporter protein activity, wherein the level of reporter protein activity indicates effectiveness of the test substance as a negative antagonist of the constitutively active G protein coupled receptor. The invention further provides a method of preventing tumor formation or cell proliferation caused by a constitutively active G protein coupled receptor. This method comprises administering an amount of the negative antagonist so identified to a subject in an amount effective to prevent tumor formation or cell proliferation.

7 Claims, 8 Drawing figures

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L7	L5 and (g protein coupled receptor or gpcr)	43	L7
L6	L5 and (g protein or gpcr)	121	L6
L5	kaposi$2 sarcoma	1841	L5
L4	L3 and g protein	0	L4
L3	L2 and gpcr	0	L3
L2	L1 and (gpcr or gprotein coupled receptor)	0	L2
L1	kaposi$1s sarcoma	42	L1

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L2	L1 and (gpcr or gprotein coupled receptor)	0	L2
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